REMARKS

1. Election/Restriction

The Examiner is thanked for rejoining claim 23. The Examiner is asked to clarify the status of claim 30. The office action mailed December 17, 2003 listed it as withdrawn. The present action did not explicitly rejoin claim 30 as it did claim 23 (see page 3 of OA), but claim 30 is listed as rejected in the office action summary, and as "under examination" on page 4. Hence, we have treated it as no longer withdrawn.

2. Definiteness

Claim 1 has been amended to supply antecedent basis for "the members" of the second level library as recited in claims 46-47, and hence the 112/2 rejection stated on page 10 should be withdrawn.

3. Enablement

In response to the enablement rejection "B", stated at pp. 5-10, claim 1 has been amended to recite MUC1, or a fragment thereof, as the "core peptide".

The Examiner concedes that the specification is enabling for "mucin1 (MUC1) as the platform" (bottom of page 5). The Examiner does not specifically address the issue of fragments of MUC1. Two such fragments, SEQ ID NO:1 (16 a.a., claim 3) and SEQ ID NO:2 (4 a.a., claim 4) are specifically claimed.

It is within ordinary skill in the art to identify a fragment of MUC1 which contains one or more O-glycosylation and/or N-glycosylation sites as taught at P6, L14-20. It is clear from P12, L3 that the contemplated fragments may be as small as a tetrapeptide.

It is respectfully submitted that the amendment overcomes

enablement rejection "B".

4. Written Description

The Examiner contends that there is a lack of written description for amended claim 1 and newly added claims 42-53. In particular, the Examiner questions the "providing" step of amended claim 1. This rejection is respectfully traversed.

Previously, claim 1 explicitly taught randomly glycosylating a "platform" (i.e., a peptide) to obtain a first level library. That step clearly provided a first level library. We chose to amend the claim to emphasize the creation of second and higher level libraries,

Claims 43 and 44 address how the first level library was provided.

Page 9, lines 10-12 provides basis for a claim to a method of making a second level library from a first level library, without explicitly reciting the first level synthesis in the claim.

The examiner does not explicitly point out what is wrong with claims 42-53, added June 17, 2004. It is difficult, of course, to defend limitations not specifically attacked. Basis for claims 42-53 is set forth below.

42: P9, L5 speaks of reaction of "a core peptide".

43: P9, L2-5 with P7, L3-11, P_, L27-33 The meaning of "a" is "one or more". If there is just one core peptide sequence, then the core peptides of all of the glycopeptides will be identical.

44: P9, L5-7.

45: See claim 42.

46: P9, L1

47: This will occur if no sites are blocked and reaction

is to completion.

48: P12, L13-14 and Table 2.

49: four amino acids long, see Example 1; mucins see P11, L15-17.

50: P11, L15-21 and P12, L3-6.

51: see Table 1, column "3". Also see P27, L9-13.

52: See Table 1, column 5 and P5, L36.

53: as for 52.

5. Prior Art Issues

The following rejections have been maintained.

(1) Claims 1-2, 5-12, 14, 17, 19-20, 22-23, 26-27 and 42-53 stand rejected as obvious over Vetter et al. (WO95/18971).

(2) Claims 1-2, 5-14, 17, 19-23 and 26-27 stand rejected as obvious over Schleyer et al.

(3) Claims 1-2, 5-14, 17, 19-22, 26-27 and 42-53 stand rejected as obvious over Rao (USP 5,795,958).

(4) Claims 3-4 stand rejected as obvious over Vetter or Rao or Schleyer in view of Ding.

It should be noted that claim 1, as presently amended, effectively combines the limitations of claims 49 and 50. Since those claims were not rejected over Schleyer, we believe that rejection is moot. Nonetheless, we will discuss Schleyer's teachings in section 4.2. below.

5.1. Vetter et al. (pp. 25-27) discloses the synthesis of glycoconjugate library of the form Ac-X-X-E(OAl)-X-P-resin, where Ac is acetyl, E is Glu, P is Pro, each X is randomly selected form a set of 18 side chain-protected AAs, and "OAl" is the allyl ester protecting group. First, a peptide library (diversity 18^4) was synthesized. Then it was converted into a glycopeptide library by removing the allyl ester and replacing it randomly

with one of a set of 17 glycosylamines (P26, L29-31); these were mono- or disaccharides.

Thus, Vetter randomly glycosylated a glycosylation site on a "platform" (peptide) to create a first level library of glycosylated platforms, per step (a) of claim 1.

However, claim 1 as amended expressly recites <u>further glycosylation</u> of the first level library to create a <u>second level library</u>.

In our specification, Scheme IV shows synthesis of the first level of a library, where Tn_1, Tn_2, Tn_3, TF_1, TF_2 or TF_3 is introduced at either of two glycosylation sites (R, R_1). Then Scheme V shows synthesis of a second level library by attachment of GlcNAc to the aforementioned Tn or TF to generate core 6_1, 6_2, 2_1, or 2_2. The key point here is that it appears that a second level library is intended to be one in which the new sugars are <u>randomly attached</u> to the <u>CHOs</u> of the first library. Such random extension of carbohydrate structure is mandatory in amended claim 1. No such step is disclosed by Vetter, so Vetter does <u>not</u> anticipate or render obvious amended claim 1.

The Examiner contends that Vetter teaches second level glycosylation at page 25, line 33 to page 27, line 10. The first level glycosylation is clearly at P26, L25-31. We are at a loss as to where the Examiner thinks a second round has occurred.

It is possible that the Examiner has been confused by P26, L5-18. The repeated steps are the monomer couplings (sequential additions of AAs) which ultimately yield the still unglycosylated glycosyl acceptor of P25, L34. See also P6, L1-25.

At the bottom of page 12, the Examiner says that our arguments concerning schemes IV and V are irrelevant because our claims are not limited to Tn or TF. The reason for describing schemes IV and V was not to justify Tn- or TF-specific claims,

but rather to explain how Applicant's first level library was randomly glycosylated to obtain a second level library. Nonetheless, in view of the Examiner's remarks, we have added new claims 54 (Tn=GalNAc) and 55 (TF).

5.2. Schleyer taught producing a glycopeptide library by glycosylation of a "preferred peptide library". The main thrust of the Schleyer article is the use of a better support, the POEPOP resin, with one of three linkers. The linker is not a randomized element. Schleyer carried out glycosylation of the peptides with one of three sugars. However, it does not appear that the sugar was randomly selected.

We previously argued that while Schleyer teaches glycosylation with one of three sugars, the sugars are not randomly selected. The Examiner acknowledges, but does not address, this point. We respectfully request that it be addressed now.

We also argued that there is no teaching, in Schleyer, of second level variation, i.e. random glycosylation of an existing carbohydrate element. This the Examiner discusses, but only in part. She directs attention to page 1976 col. 1, which says that "free hydroxyl groups on the oligosaccharide moiety could be glycosylated with different glycosyl trichloroacetimidates". Yes, this is second level glycosylation, but it is not random unless the glycopeptide is reacted with a mixture of the different glycosyl trichloroacetimidates.

It should be noted, for the sake of clarity, that at this point Schleyer is referring to the prior work of references 6 (Paulsen, et al. 1997) and 8 (Yani et al. 1994) (Schleyer was a co-author of reference 6).

In the experiment described directly in Shleyer et al., there was no carbohydrate variation at all. In Scheme 1, the

same peptide substrate (Ile-Ser-Gly-Ile-Gly), bearing one of three linkers (a, b, c), was glycosylated at the Serine side chain with a single carbohydrate structure, perbenzoylated galactopyranosyl trichloroacetimidate (**2**). The protected glycopeptide (3a-3c) was then deprotected (4a, 4b). All peptides received the same carbohydrate structure at the same site, so there was no "glycodiversity".

Finally scheme 3 shows synthesis of a small nonrandom library of glycopeptides. Schleyer started with "four different octapeptide templates with two different glycosyl acceptor sites. The peracetylated trichloroacetimidates of L-fucose and D-galactopyranose were used in two sequential glycosylation steps to produce the four different unprotected glycopeptides..."

The choice of R1 and R2 in the templates foreordained which sugars would be coupled at those sites, as reactants a-f were sequentially introduced, thereby also sequentially, but at R1/R2-determined sites, introducing the sugars (the Gal by "c", the Fuc by "e"). Thus, the glycosylation was not random. In scheme 3, there was no reaction of one sugar with another, hence, no second level glycosylation. What we have in Schleyer scheme 3 is a nonrandom first level glycopeptide library.

5.3. Rao creates a glycopeptide library using fucose-serine building blocks. No amino acid other than serine is glycosylated. Rao only claimed the fucosylation of serine. At col. 3, lines 36-44, he discloses glycosylation (not just fucosylation) of serine, threonine, tyrosine, hydroxyproline, homoserine, hydroxylysine, asparagine and glutamine. That admitted, there is still no suggestion of random glycosylation. Rather, the randomness is in the amino acid sequence of the peptide. Indeed, col. 3, lines 9-22 appear to contrast the nonrandomness of the carbohydrate with the randomness of the

peptide.

The Examiner seeks to overcome this problem by reference to prior art cited by Rao, notably Peters et al. (1992), cited at col. 2, lines 55-60. The citation refers to use of protected Ser and Thr building blocks, but does not say what sugars were attached, and whether the sugars were randomized. (We have previously stated that if the Examiner wishes to rely on Peters, it should be cited and made of record.)

To expedite prosecution, we have reviewed Peters, et al., J. Chem. Soc. Perkin Trans. 1:1163 (1992). This describes stepwise solid-phase synthesis of glycopeptides using already glycosylated amino acids as building blocks. Only one carbohydrate structure (GalNAc) was employed.

A multiple column peptide synthesizer was used for simultaneous assembly of forty different glycopeptides. These glycopeptide varied in amino acid sequence (see Fig. 1), and hence in the location of the carbohydrate structures, but the only carbohydrate structure employed was GalNAc. There was no randomization of the carbohydrate structures.

The Examiner's response (first full paragraph, OA page 15) has confused the teachings of Rao with those of Peters et al. (1992). See the discussion on page 14 of our June 17, 2004 amendment. A rejection, nominally over Rao, which relies on the teachings of Peters (never made of record, although cited by the Examiner, bottom of page 11, OA of December 17, 2003) is plainly improper. For the sake of good order, we have submitted an IDS to make Peters of record. We have also made a later Peters article (1995) of record.

5.4. The Ding reference discloses that certain peptides (SP-KLH, SP1-6, and SP1-5) derived from MUC1 can elicit a cellular immune response, and peptides SP1-7-KLH, SP1-5 and SP1-6

inhibit tumor growth given alone or in combination with cyclophosphamide (Tables 4 and 5). However, these were synthetic, unglycosylated peptides (p. 10, col. 2). Hence, it appears to teach away from glycosylation, as these peptides corresponds to portions of MUC1 which are potentially glycosylated. The article notes that "cancer-associated mucins are also known to be under-glycosylated" (p. 9, col. 2).

Respectfully submitted,

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